Toxicology:

Modern toxicology goes beyond the study of the adverse effects of exogenous agents to the study of molecular biology of cell, using toxicants as tools, and studying the mechanisms of endogenous compounds such as oxygen radicals and other reactive intermediates generated from xenobiotics and endobiotics.

We are exposure to chemicals and the public health aspects are effect with chemicals in air, water, other parts of the environment, food, and drugs, so that toxicologists have been intimately involved in the discovery and development of new drugs, food additives, and pesticides. Toxicologists also participate in the development of standards and regulations designed to protect human health and the environment.

The disposition of xenobiotic: is the composite actions that determines its concentration at the site of action of, it include absorption, distribution, biotransformation, and elimination, that dictates the potential for adverse events to occur. The various factors and organs involved in affecting disposition of a toxicant.

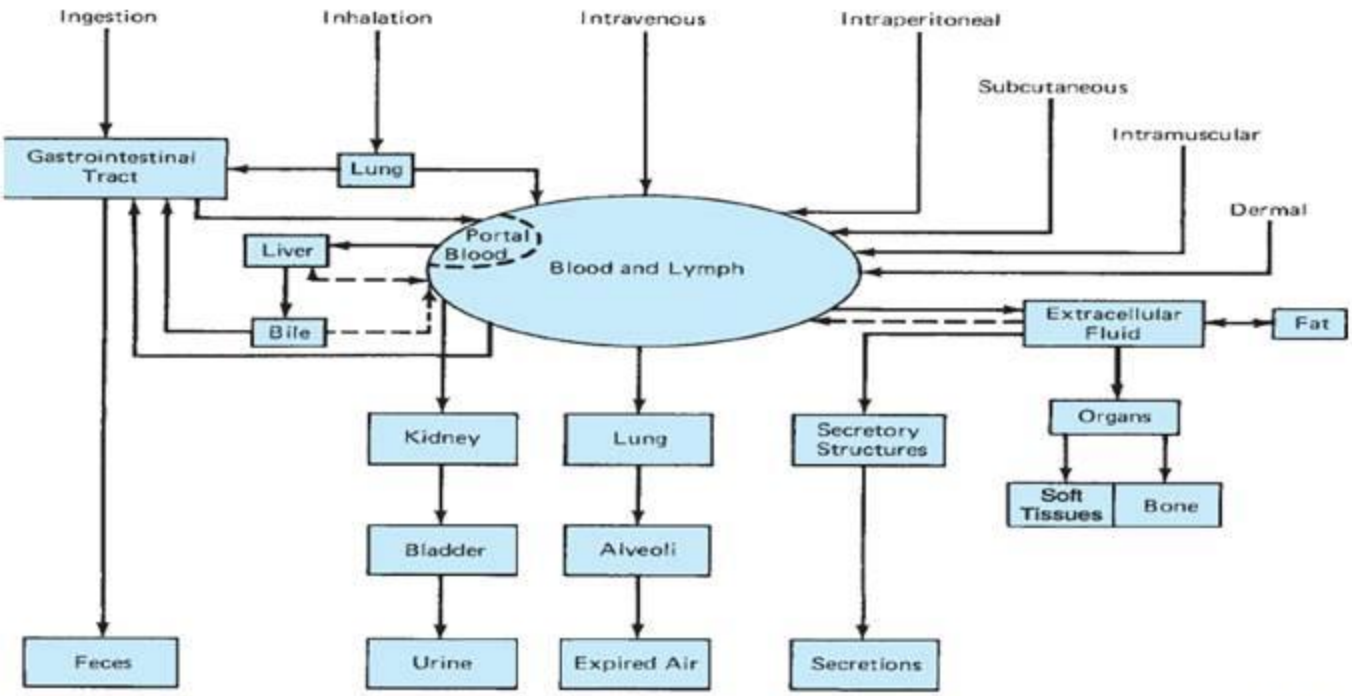

Figure 5-1. Summary of the disposition of toxicants as determined by absorption, distribution, and excretion in the body.

The skin, lungs, and alimentary canal are the main barriers that separate organisms from an environment containing chemicals. Toxicants must cross one or several of these incomplete barriers to exert deleterious effects, A chemical absorbed into the bloodstream or lymphatics through any of the major barriers then distributed at least to some extent, throughout the body, including the site where it produces damage. This site is called the target organ or target tissue.

Factor that can influence the susceptibility of organs to toxicants

-1Target organ concentration)example of this distinction is dichlorodiphenyltrichloroethane (DDT), that achieves high concentrations in fat depots but is not toxic to that tissue.(

-2Poor absorption of a toxicant, resulting prevents toxicity because never attain a sufficiently high concentration to cause toxicity.

-3Rapidly biotransformed or eliminated from an organism, it is less likely to be toxic because the rapid excretion prevents it from reaching a sufficiently high concentration to cause toxicity.

CELL MEMBRANES

Toxicants usually pass through a number of cells, such as the stratified epithelium of the skin, the thin cell layers of the lungs or the gastrointestinal (GI) tract, capillary endothelium, and ultimately the cells of the target organ.

The fluid character of membranes is determined largely by the structure and relative abundance of unsaturated fatty acids. Toxicants cross it by facilitating, active or passive transport.

-1**The toxicant can across the membrane by:**

Lipid solubility: the rate of transport across membranes correlates with lipid solubility ، the toxicants are organic molecules with differing degrees of lipid solubility (solution are ionized according to Arrhenius' theory: The ionized form usually has low lipid solubility and thus does not permeate readily through the lipid domain of a membrane. The rate of transport of the nonionized form is proportional to its lipid solubility.(

-2Aqueous pores: there may be some transport of organic anions and cations (depending on their molecular weight) through the aqueous pores, but this is a slow and inefficient process.

-3Toxicant can Passage through channels this process is called filtration, as it involves bulk flow of water caused by hydrostatic or osmotic force. One of the main differences between various membranes is the size of these channels. The systems are responsible for the transport (both influx and efflux) across cell membranes Based on the sequencing of the human genome, However, not all of these genes contribute to the disposition of toxicants.

-4Active transport is characterized by:

a) movement of chemicals against electrochemical or concentration gradients ،

b) saturability at high substrate concentrations،

c) selectivity for certain structural features of chemicals،

d) competitive inhibition by chemical congeners or compounds that are carried by the same transporter،

e) requirement for expenditure of energy, so that metabolic inhibitors block the transport process.

Xenobiotic transporter:

-1The gene conferred multidrug resistance (MDR) to the cells, and was also called P-glycoprotein (P-gp).This transporter functions as an efflux pump, which in cancerous cells, exudes cytotoxic. In humans, the major form of P-gp involved in xenobiotic transport is a single protein (MDR،(1

-2Transport proteins known as ATP-binding cassette (ABC) transporters. The second important ABC transport subfamily is the multi resistant drug protein (MRP) family function predominantly as facilitative transporters.

-3A major family of such transporters is known as solute carriers (SLCs). SLC families play important roles in the disposition of endogenous compounds, including glucose ، neurotransmitters, nucleotides, essential metals, and peptides. Additionally, there are several families that are vital to xenobiotic disposition, regulating the movement of many diverse organic anions and cations across cell membranes.

-4The organic-anion transporting peptides (OATP, SLCO family) are important membrane transport proteins that mediate the sodium-independent transport of a wide range of compounds, including organic acids, bases the mechanism of transport is anion exchange such that the cellular influx of an organic compound is thought to be coupled to the efflux of bicarbonate, glutathione, or glutathione conjugates.

-5The organic-anion transporter (OAT; SLC22) family is particularly important in the renal uptake of anions, and four human proteins (OAT1, 2, 3, and 4) have been identified in the kidney, OATs transport substrates against an electrochemical gradient in exchange for intracellular dicarboxylates،

-6Peptide transporters (PEPT1 and PEPT2) are responsible for the transport of di- and tri-peptides as well as drugs and toxicants such as the β-lactam antibiotics. Facilitated Diffusion applies to carrier mediated transport that exhibits the properties of active transport except that the substrate is not moved against an electrochemical or concentration gradient, and the transport process does not require the input of energy ؛ that is, metabolic poisons do not interfere with this transport.

ABSORPTION

The process by which toxicants cross body membranes and enter the bloodstream is referred to as absorption. Xenobiotics penetrate membranes during absorption by the same processes as do biologically essential substances.

The main sites of absorption are the GI tract, lungs, and skin. However, absorption may also occur from other sites, such as the subcutis, peritoneum, or muscle, if a chemical is administered by special routes.

A.Enteral administration includes all routes pertaining to the alimentary canal)sublingual, oral, and rectal.(

B. Parenteral administration involves all other routes (intravenous, intraperitoneal ، intramuscular, subcutaneous, etc.(.

Absorption of Toxicants by the Gastrointestinal Tract

Many environmental toxicants enter the food chain and are absorbed together with food from the GI tract. This site of absorption is also particularly relevant to toxicologists because accidental ingestion is the most common route of unintentional exposure to a toxicant (especially for children) and intentional overdoses most frequently occur via the oral route.

Factors effect on the absorption of toxicant

(1If a toxicant is an organic acid or base, it tends to be absorbed by simple diffusion in the part of the GI tract where it exists in its most lipid-soluble (nonionized) form . Because gastric juice is acidic and the intestinal contents are nearly neutral, the lipid solubility of weak organic acids or bases can differ markedly in these two areas of the GI tract. One can determine by the Henderson–Hasselbalch equations the relation between the fraction of toxicant in nonionized (lipid-soluble) form and estimate the rate of absorption from the stomach or intestine. According to this equation weak organic acids are absorbed more readily from the stomach than from the intestine. In contrast, organic bases that the absorption of such compounds occurs predominantly in the intestine rather than in the stomach.

(2surface area

(3blood flow rate

(4Particles size: most toxicants enter the body by simple diffusion. The lipid-soluble substances are absorbed by this process more rapidly and extensively than are water - soluble substances. Particles size is inversely related to absorption such that absorption increases with decreasing particle diameter.

There are numerous additional factors relating to the GI tract itself that influence the absorption of xenobiotics. These factors include:

- 1Chemical resistance or lack of resistance to alteration by the acidic pH of the stomach، enzymes of the stomach or intestine،
- 2The presence of food،
- 3Digestive enzymes: snake venoms are much less toxic by the oral route relative to intravenous exposure because they are broken down by digestive enzymes of the GI tract.
- 4Bile acids،
- 5Bacterial microflora in the GI tract, a variety of nitroaromatic compounds are reduced by intestinal microflora to potentially toxic and carcinogenic aromatic amines

-6The motility and permeability of the GI tract, some agents used as laxatives alter absorption of xenobiotics by increasing intestinal motility whereas agents used as antidiarrheals may increase absorption by slowing intestinal motility.

-7Agents such as the chelator effect of ethylenediaminetetraacetic acid (EDTA) by the binding of calcium, that increase absorption of some toxicants by increasing intestinal permeability reduces the integrity of the cell junctions. EDTA and other chelators increase the lipid solubility and thus the absorption of complex ions.

-7Presystemic elimination or first-pass effect is referred to a chemical before enters the systemic circulation, it can be biotransformed by the cells in the GI tract or extracted by the liver and excreted into bile with or without prior biotransformation.

There are other factors have been shown to alter absorption, lead and many other heavy metal ions are not absorbed readily from the GI tract, metal ions can affected on absorption of other ions. For example, cadmium decreases the absorption of zinc and copper, calcium decreases cadmium absorption, and magnesium decreases absorption of fluoride.

Grapefruit juice increases the GI absorption of numerous pharmaceutical agents (such as calcium-channel blockers and cholesterol-lowering agents) and in some cases, this effect leads to toxic or adverse reactions resulting from increased exposure to the drugs .

Absorption of Toxicants by the Lungs

Toxic responses to chemicals can occur from absorption following inhalation exposure. A major group of toxicants that are absorbed by the lungs are gases (e.g., carbon monoxide, nitrogen dioxide, and sulfur dioxide), vapors of volatile or volatilizable liquids)e.g., benzene and carbon tetrachloride), and aerosols.

When inhaled, gases first pass through the nose, filtering through simple epithelial-lined turbinates, which serve to increase the surface area of exposure. Because the mucosa of the nose is covered by a film of fluid, gas molecules can be retained by the nose and not reach the lungs if they are very water soluble or react with cell surface components. Therefore, the nose acts as a —scrubber‖ for water-soluble gases and highly reactive gases, partially protecting the lungs from potentially injurious insults. The lung can also contribute to the biotransformation or elimination of chemicals before their entrance into the systemic circulation. Absorption of gases in the lungs differs from intestinal and percutaneous three reasons for this.

•First, ionized molecules are of very low volatility, so that they do not achieve significant concentrations in normal ambient air.

•Second, the epithelial cells lining the alveoli—that is, type I pneumocytes—are very thin and the capillaries are in close contact with the pneumocytes, so that the distance for a chemical to diffuse is very short.

•Third, chemicals absorbed by the lungs are removed rapidly by the blood, and blood moves very quickly through the extensive capillary network in the lungs.

As the contact of the inspired gas with blood continues in the alveoli, more molecules dissolve in blood until gas molecules in blood are in equilibrium with gas molecules in the alveolar space. —Equilibrium, the ratio of the concentration of chemical in the blood and chemical in the gas phase is constant‖. The solubility ratio is called the blood-to-gas partition coefficient —the ratio of the concentration in blood to the concentration in gas that is in contact with that blood, when the partial pressure in both compartments is equal‖, and it is unique for each gas. The higher inhaled concentration of a gas (i.e., the higher the partial pressure), lead the higher the gas concentration in blood, but the blood : gas ratio does not change unless saturation has occurred. For example, chloroform has a relatively high blood to-gas partition coefficient (approximately 20), whereas ethylene has a low coefficient (0.14). By comparison, a smaller percentage of the total ethylene in the lungs is removed into the blood during each circulation because the low blood-to-gas partition coefficient dictates that blood is quickly saturated with this gas. Therefore, an increase in the respiratory rate or minute volume does not change the transfer of such a gas to blood.

In contrast, with high blood to-gas partition coefficient and increase in the rate of blood flow lead to increases the rate of uptake of a compound with a low solubility ratio. The more soluble a toxic agent in blood, the more of it will be dissolved in blood by the time equilibrium is reached.

In each tissue, the gas molecules are transferred from the blood to the tissue until equilibrium is reached at a tissue concentration dictated by the tissue-to-blood partition coefficient. After releasing part of the gas to tissues, blood returns to the lungs to take up more of the gas. The process continues until a gas reaches equilibrium between blood and each tissue according to the tissue-to-blood partition coefficients characteristic of each tissue.

Aerosols and Particles Absorption of aerosol and particles is distinguished from gases and vapors by the factors that determine absorption from the inhalation route of exposure . The absorption after exposure to aerosols are determined by the aerosol size and water solubility of any chemical present in the aerosol.

The aerosols deposited on the unciliated anterior of the nose tend to remain at the site of deposition until they are removed by nose wiping, blowing, or sneezing. The mucous blanket of the ciliated nasal surface propels insoluble particles by the movement of the cilia. particles inhaled through the mouth are swallowed within minutes.

Soluble particles may dissolve in the mucus and be carried to the pharynx or may be absorbed through the nasal epithelium into the blood so that toxicants or viral infections that damage cilia may impair the efficiency of this process.

These extremely small particles may be absorbed into blood or cleared through the lymphatics after being scavenged by alveolar macrophages.

Removal or absorption of particulate matter from the alveoli to occur by three major mechanisms:

•First, particles may be removed from the alveoli by a physical process. It is thought that particles deposited on the fluid layer of the alveoli are aspirated onto the mucociliary escalator of the tracheobronchial region. From there, they are transported to the mouth and may be swallowed.

•Second, particles from the alveoli may be removed by phagocytosis. These phagocytic cells are found in large numbers in normal lungs and contain many phagocytized particles of both exogenous and endogenous origin.

•Third, removal may occur via the lymphatics. The endothelial cells lining lymphatic capillaries are permeable to very large molecules.

The lymphatic system plays a prominent role in collecting high-molecular-weight proteins leaked from cells or blood capillaries and particulate matter from the interstitium and the alveolar spaces. Particulate matter may remain in lymphatic tissue for long periods, and this explains the phenomenon of —dust store of the lungs‖.

Some particles may remain in the alveoli indefinitely. This may occur when long-lived alveolar macrophages phagocytose indigestible dust particles and secrete cytokines that stimulate the development of a local network of type I and III collagen fibers to form an alveolar dust plaque or nodule.

Absorption of Toxicants Through the Skin

Human skin comes into contact with many toxic chemicals, but exposure is usually limited by its relatively impermeable nature. However, some chemicals can be absorbed by the skin in sufficient quantities to produce systemic effects. For example, there are several insecticides for which fatal exposures have occurred in agricultural workers after absorption through intact skin. In addition, there are numerous chemicals that increase tumor development in other organs after dermal application. The complex process involves dehydration and polymerization of intracellular matrix forming keratin filled dried cell layers. During the process, the cell walls apparently double in thickness and transform to a dry, keratinous semisolid state with much lower permeability for diffusion of toxicants. The stratum corneum is unique anatomically and represents the single most important barrier to preventing fluid loss from the body while also serving as the major barrier to prevent the absorption of xenobiotics into the body.

The dermis is situated beneath the epidermis; This region also contains the vascular network that serves to carry absorbed compounds into the body. Ultimately, to be absorbed a chemical must pass the barrier of the stratum corneum and then traverse the other layers of the skin.

In general, lipophilic compounds are absorbed more readily across the stratum corneum by passive diffusion, whereas the penetration of hydrophilic compounds is more limited . Nonpolar toxicants diffuse through the skin in a manner that is proportional to their lipid solubility and inversely related to molecular weight.

Human stratum corneum displays significant differences in structure and chemistry from one region of the body to another, and these differences affect the permeability of the skin to chemicals. The permeability of the skin also depends on both the diffusivity and the thickness of the stratum corneum.

There are several factors that can influence the absorption of toxicants through the skin ، including:

(1)The integrity of the stratum corneum, removal of this layer by Caustic agents causes a dramatic increase in the permeability of the epidermis for a variety of large or small molecules.

(2)The hydration state of the stratum corneum. Water plays an extremely important role in skin permeability. Under normal conditions, the stratum corneum is partially hydrated ، This amount of water increases the permeability of the stratum corneum approximately -10fold over the permeability that exists when it is completely dry.

(3)Temperature, increased absorption for both lipid-soluble and water-soluble toxicants ، and an increase in temperature will increase dermal penetration by increasing dermal blood flow.

(4)Solvents as carriers solvents used to dissolve compounds of interest can also influence dermal penetration. In general, lower absorption will be observed if a toxicant is highly soluble in the vehicle, whereas low solubility of the toxicant in the vehicle will tend to increase dermal penetration. In addition, solvents such as dimethyl sulfoxide)DMSO) facilitate the penetration of toxicants through the skin by increasing the permeability of the stratum corneum. DMSO:

I. removes much of the lipid matrix of the stratum corneum, making holes on artificial shunts in the penetration barrier؛
II. reversible configuration changes in integral protein structure of water molecules transporter؛
III. produces functions as a swelling agent .

(5)molecular size.

(6)Biotransformation reactions in skin can also facilitate absorption, and the presence of metabolizing enzymes is highly variable across species.

Effect the route of administration on toxicant

The toxicity of a chemical may depend on the route of administration. The most common routes are: